

Adverse effects of long-term amiodarone therapy

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Amiodarone, first used in Europe for the treatment of angina pectoris in the 1960s, began to be widely utilized as an antiarrhythmic agent in the 1970s. Currently, it is one of the most commonly used antiarrhythmic agents for the treatment of almost all tachyarrhythmias; however, frequent occurrence of adverse effects is an important concern when deciding on its use.

In the current issue of *The Korean Journal of Internal Medicine* [1], type and frequency of adverse effects are reported among a relatively large number of amiodarone treated patients (n = 930) from a single institution. At mean follow-up of 2.7 years, 16.6% of patients experienced amiodarone related adverse effects and 15.1% had to discontinue the drug because of adverse effects.

The incidence of adverse effect was reported as high as 70% with 18% to 37% rate of adverse effect driven drug discontinuation at 5 years follow-up. The results of the article in this issue of the journal appear consistent with those in a practical guide published in 2007, with incidence of adverse effects of 15% during first year of amiodarone use increasing to up to 50% during long-term use [2]; there was higher frequency of adverse effects in patients on amiodarone for a long time which was amenable to reversal by dose lowering or drug dis-

continuation.

Rate of drug discontinuation secondary to drug adverse effects in the study in this issue; however, appears lower than the 22.9% rate reported in 1997 in a meta-analysis of low dose (daily average of 152 to 330 mg) amiodarone therapy for at least 1 year [3]. As pointed out by the authors, the study in this issue was retrospective and mild adverse effects might have been missed or not recorded.

Pulmonary toxicity is one of the fatal adverse effects of amiodarone with mortality as high as 10% and incidence of approximately 2% in previous studies, even higher among older patients on higher doses [4]. Pulmonary toxicity manifests with dyspnea, cough, fever, and pulmonary lesions usually progress if early detection is not made [5]. For early detection of pulmonary toxicity, pulmonary function tests including diffusion capacity and chest X-ray are recommended every 3 months during the first year and twice yearly thereafter, or if not possible, at least chest X-ray once yearly. In principle, the drug should be discontinued if pulmonary toxicity is detected and corticosteroid used for significant toxicity.

Amiodarone is an iodinated derivate of benzofuran similar in structure to the thyroid hormones triiodothyronine (T₃) and thyroxine (T₄), and containing a large of amount of iodine; spe-

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cifically, a 100 mg tablet contains 250 times the daily iodine requirement. Because of the latter features, use of amiodarone may cause thyroid damage and induce hypothyroidism with thyroid stimulating hormone (TSH) elevation in 2% to 4% of cases or hyperthyroidism with mainly increased T₃ level in 1% to 2% of cases [6]. Amiodarone treatment can initially elevate levels of TSH and free and total T₄ while decreasing those of total and free T₃. After achieving equilibrium at 3 months TSH is normalized while T₄ and T₃ remain at high and low normal levels, respectively. To detect such changes, thyroid function testing is recommended every 3 months during the first year and once or twice yearly thereafter [2]. Amiodarone can cause bradycardia and conduction disturbance by depression of sinus or atrioventricular node and prolongation of myocardial refractoriness. In the article in this issue, frequency of these adverse effects was approximately 9.6% rendering them the most frequent, in contrast to the 3.3% to 5% reported in the meta-analysis of low dose amiodarone [2]. These adverse effects can occur more frequently if patients are older or have structural heart disease.

Amiodarone through a direct drug effect causes prolongation of QT interval in almost all patients. Minimal QT prolongation after amiodarone treatment is not clinically significant, and in previous meta-analysis, low dose amiodarone use was associated with very small risk of severe QT prolongation and torsades de pointes [3].

The most common ocular change after long-term use of amiodarone is corneal epithelial opacities in 70% to 100% patients followed by lens opacities in 50% to 60% of patients. However, these changes do not affect eyesight and therefore drug discontinuation is not warranted. In rare cases of retinopathy or optic neuropathy, lowering dose or discontinuation of amiodarone should be considered [7]. The study in this issue reports a very low frequency of 0.6% of ocular adverse events as compared to previous studies, again likely reflecting capture of serious adverse effects and not minor ones not affecting eyesight. A practical guide does not recommend regular eye examinations in patients without ocular symptoms [2].

Although it was not mentioned in the paper in this issue, amiodarone can cause other adverse effects including asymptomatic elevation of liver enzyme, neurologic

dysfunction, photosensitivity, bluish skin discoloration, and gastroenterological disturbance. Further additional examinations are recommended if symptoms suggesting these adverse effects are shown in patients. Routine liver function test on a regular basis (every 6 weeks after amiodarone treatment) is recommended in the practical guide [2].

In Keimyung University Dongsan Medical Center, 876 patients who had taken amiodarone regularly over 3 months were retrospectively investigated [8]. Overall incidence of adverse effects was 11.0% (69 patients) after an average of 24 months of amiodarone treatment. Hypothyroidism (60 patients, 6.9%) was the most common adverse effect followed by ocular (20 patients, 2.3%), pulmonary (10 patients, 1.1%), and skin adverse effect (six patients, 0.7%). Different incidence of adverse effects between the latter study and that in this issue is probably secondary to different treatment dose and duration.

Dronedarone is a new antiarrhythmic agent for the treatment of atrial fibrillation and flutter. Dronedarone exhibits similar pharmacological action to amiodarone but iodine was eliminated to reduce toxicity including pulmonary and thyroid toxicity. In the ATHENA study [9], use of dronedarone in paroxysmal or persistent atrial fibrillation patients with moderate risk of cardiovascular events significantly reduce cardiovascular events including unplanned cardiovascular hospitalization and all-cause mortality. The DIONYSOS study [10] compared dronedarone (400 mg twice daily) and amiodarone (600 mg daily for 28 days, and 200 mg daily thereafter) over 6 months in terms of maintenance of sinus rhythm in atrial fibrillation patients. Recurrence rates of atrial fibrillation were 63% and 42% in the dronedarone and amiodarone groups, respectively, indicating less potency of dronedarone on sinus rhythm maintenance. However, through 7 months follow-up, dronedarone was associated with significantly less side effects and therefore with lower discontinuation rate. Thus, one could argue that dronedarone has a better safety profile even though it has decreased efficacy in preventing atrial fibrillation. However, dronedarone increases mortality in heart failure patients with NYHA class III/IV and permanent atrial fibrillation patients. Therefore, it is recommended that dronedarone be avoided in patients with heart failure or permanent atrial fibrillation.

Taken altogether, there seems to be small risk of either minor/fatal adverse effects or death with low doses of amiodarone (less than 200 mg per day). However, it is important to keep in mind that long-term treatment of amiodarone is associated with occurrence of adverse effects warranting regular follow-up examinations for their early detection.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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